Respiratory Rate as a Factor in Lung Injury—Not Just What You Set, but How You Set

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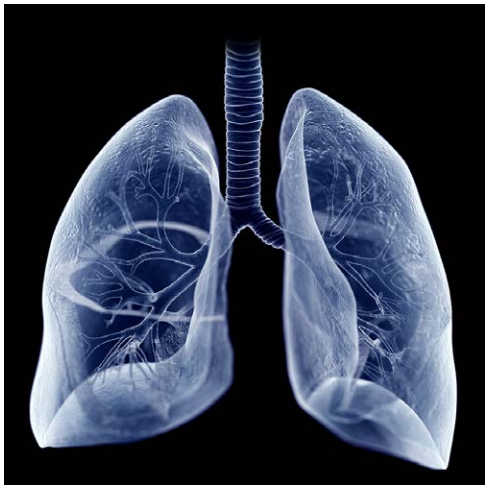
Respiratory support with mechanical ventilation is crucial for critically ill patients with diseases such as acute respiratory distress syndrome (ARDS), in which the pulmonary gas exchange capacity is impaired. However, ventilation itself exposes the lungs to a nonphysiologic environment, which in itself injures the lungs. Reports on ventilator settings that have been shown to affect patient outcomes have focused on low tidal volume (V_T)[1] and adequate driving pressure.[2] Additionally, the concepts of pressure (barotrauma), V_T (volutrauma), and cyclic opening–closing of the lung units (atelectrauma) have been proposed as mechanisms of ventilation-induced lung injury. Ventilator settings that minimize each of these factors were subsequently studied and discussed. Although the respiratory rate is an essential item in the ventilator setting, it has received little attention because it is passively adjusted after the V_T setting. Animal studies have shown that increasing the respiratory rate exacerbates ventilation-induced lung injury,[3] and evidence in support of this phenomenon is gradually accumulating. Based on the recognition that the severity of lung injury is affected by the number of static lung injury factors applied to the lung tissue over a certain period of time, the concept of mechanical power (consisting of volume, pressure, flow, and respiratory rate) was proposed to quantify these factors. These dynamic factors are the cause of so-called "ergotrauma," in contrast to other static factors.[4] Thus, the respiratory rate is gaining attention as a dynamic factor; however, there are still few reports describing how specific respiratory rate settings affect lung injury.



"Although the respiratory rate is an essential ventilator setting, it has received little attention [regarding] ventilation-induced lung injury."

In this issue of Anesthesiology, Xavier *et al.*[5] published an interesting study that may add some insights to this field. The authors addressed the hypothesis that lung injury induced by mechanical ventilation with a high respiratory rate would be attenuated if the desired respiratory rate was reached by gradual rather than abrupt increases. In an experimental model of mild ARDS induced by intratracheal administration of lipopolysaccharide, the authors randomly assigned rats to receive mechanical ventilation (pressure control mode to maintain a V_T of 6 ml/kg with 3 cm H_2O positive end-expiratory pressure) with various respiratory rate patterns for a total of 2 h. In the abrupt increase group, the respiratory rate was abruptly increased from 70 to 130 breaths/min, while in the gradual adaptation group, the respiratory rate was gradually increased from 70 to 130 breaths/min in 30 or 60 min. In each group, the authors evaluated pathologic findings of lung injury after 1 h of ventilation at 130 breaths/min, heterogeneity scores of lung aeration, inflammatory mediators, and markers of cellular damage. In another series, an additional group underwent a pulmonary recruitment maneuver (continuous positive airway pressure of 30 cm H_2O for 30 s) before the respiratory rate was abruptly increased from 70 to 130 breaths/min. The authors found that the abrupt increase in the respiratory rate resulted in a greater histologic lung injury score, worse lung aeration heterogeneity, and higher levels of markers of inflammation and cellular damage. In the gradual adaptation group, all of these changes were attenuated. Additionally, the lung recruitment maneuver before the abrupt increase in the respiratory rate prevented the increase in the markers of inflammation and cell damage after mechanical ventilation with a high respiratory rate.

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This study highlights two particularly novel points. First, a gradual change in the respiratory rate from 70 to 130 breaths/min was associated with a lower degree of histologic lung injury and lower expression of inflammatory mediators and tissue damage indicators compared with an abrupt change in the respiratory rate, despite the fact that the cumulative mechanical power values were higher. The best explanation for this finding would appear to be that factors other than those comprising mechanical power affect lung injury (in the current study, such a factor may have been the speed at which the respiratory rate changed).

When alveolar epithelial cells undergo mechanical stretch *in vitro*, larger magnitudes and higher numbers of stretch cycles are associated with greater cell death. However, when the rate of change before maximum deformation is reduced, cell death is less likely, even when the maximum expansion is the same.[6] Furthermore, another cell-based study showed that lung cells recover very quickly from damage.[7] Therefore, giving cells a chance to recover by making gradual rather than sudden large changes in the respiratory rate may reduce cell death and consequently reduce lung injury. This speculation appears to fit well with the mechanism suggested by the current results and should be proven in future studies.

Second, in the additional experiments, the previous recruitment maneuver reduced or nearly canceled the lung injury (inflammatory response, epithelial cell damage) caused by the abrupt increase in the respiratory rate. This suggests that the abrupt increase in the respiratory rate from 70 to 130 breaths/min caused lung injury by the phenomenon of "baby lung," defined as overdistension of the normally aerated alveolar units. A recruitment maneuver may decrease the fraction of nonaerated alveolar units, which may in turn decrease regional tidal strains and heterogeneity. A recruitment maneuver may work to open atelectatic alveoli, improve lung aeration heterogeneity, and increase the effective tidal ventilation volume, although its routine application in ARDS is not recommended because of its lack of association with improved survival in a multicenter randomized controlled clinical trial.[8] Further research is needed to determine whether adaptation of the respiratory rate has the same effect as a recruitment maneuver as well as to elucidate its mechanism.

This study provides some interesting data for clinical application. The supplemental digital content shows that the Pao_2/Fio_2 ratio was highest in the group that underwent an abrupt increase in the respiratory rate for 2 h; the lung injury was histologically most severe in this group. These results indicate that pathologic abnormalities precede blood gas abnormalities. Methods with which to assess the heterogeneity of pulmonary aeration in clinical practice are limited, but the use of electrical impedance tomography may be a possible solution. The ability of electrical impedance tomography to assess ventilation heterogeneity has been reported in a porcine model of lipopolysaccharide-induced acute lung injury[9] and in patients with ARDS on mechanical ventilation.[10] If electrical impedance tomography were sensitive enough to detect abnormalities in lung aeration heterogeneity before the appearance of blood gas abnormalities, a more appropriate ventilator setting could be implemented. The results of further clinical studies are anticipated.

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Competing Interests

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